Clinical update on the first-in-human trial of SYS6002 (CRB-701), a next-generation, Nectin-4 targeting, MMAE bearing, antibody drug conjugate

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Background

- Linker-conjugation of an ADC is a key feature in optimizing highly active and well tolerated agents
- For maximal intra-tumoral delivery, linkers need to be highly stable in the systemic circulation yet allow for efficient drug release at the target site
- SYS6002 (CRB-701) is a next-generation Nectin-4 ADC that uses novel, site-specific, cleavable transglutaminase conjugation technology[1]
- It is designed to overcome dose-limiting toxicities associated with the maleimide conjugation (linker-payload) used by enfortumab vedotin (EV)
- Non-clinically, SYS6002 (CRB-701) demonstrates preferential internalization-mediated payload release and a longer half-life[2]
- Allometric scaling predicts an effective human dose ≥ 2.8 mg/kg
- Dose escalation of a Q3W schedule is ongoing and aims to reduce the concentration of free-MMAE and related dose limiting toxicities peripheral neuropathy (PN) and skin rash[3]
- These adverse events lead to dose interruptions (61%), reductions (34%), and discontinuations (17%) of EV [4]

Nonclinical validation

SYS6002 vs. EV in NHPs

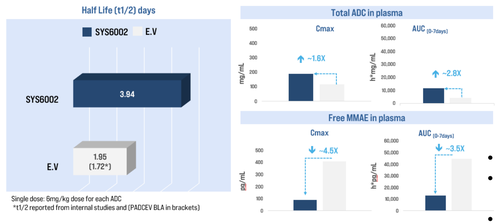


Figure 1: Comparison of SYS6002 (CRB-701) vs. enfortumab vedotin exposures over 7 days after a single dose in non-human primates. SYS6002 (CRB-701) is designed to increase the ADC half life and reduce circulating concentration of free-MMAE[2]

SYS6002 (CRB-701)

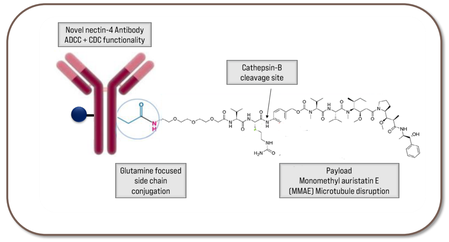


Figure 2: Design of SYS6002 (CRB-701) a next-generation Nectin-4 targeting ADC. With a site-specific cleavable linker, a homogenous DAR and a novel Nectin-4 targeting monoclonal antibody

Method

SYS6002-001 Dose Escalation

KEY ELIGIBILITY

Age ≥18 years
Advanced urothelial carcinoma or Nectin-4 positive
Advanced solid tumors
ECOG 0-1
Adequate organ function
No uncontrolled diabetes
No active CNS metastasis

ESCALATION DESIGN

Bayesian Optimal Interval (BOIN) design with accelerated titration at DL-1
IV Q3W over a 21-day cycle
0.2 mg/kg
0.6 mg/kg
1.2 mg/kg
1.8 mg/kg
2.7 mg/kg
3.6 mg/kg
4.5mg/kg (recruiting)

KEY END POINTS

- Safety / tolerability
- Pharmacokinetics
- Anti tumor activity

NEXT STEPS

- Continue escalation
- PK expansion at 3.6mg/kg
- MTD or RP2D
- Specific expansion

Figure 3: SYS6002-001 first-in human study design and associated dose escalation schema

- Escalation spanned 7 dose levels 0.2, 0.6, 1.2, 1.8, 2.7, 3.6, 4.5 mg/kg
- Dose escalation decisions were governed by a Bayesian Optimal Interval (BOIN) design with accelerated titration at DL-1
- The primary aim is to evaluate safety and tolerability of SYS6002 (CRB-701) and determine the Maximum Tolerated Dose (MTD) and/or the Phase II dose in patients with advanced solid tumors who have failed or were intolerant to standard treatment
- The pharmacokinetic (PK) and preliminarily anti tumor activity of SYS6002 (CRB- 701) has also been assessed

Results

Demographics & Key Characteristics

Characteristic	Value	Characteristic	Value
Median age (range)	55 (35,76)	Primary tumor type	n=37
Sex (M/F)	29.7%, 70.3%	Urothelial	13
ECOG PS 0,1, missing	8.1%, 89.2%, 2.7%	Cervical	15
Weight in Kg mean (range)	59.01 (36.0, 84.9)	TNBC/Breast	5
Prior therapies median (range)	4.0 (0,10)	CRC	1
Creatinine clearance <60µ mol/L	29.7%	Esophageal	2
Visceral metastasis (Y/N/missing)	73%, 8.1%, 18.9%	Not assigned/missing tumor type	1
HbA1c <6.5%	97.3%		

Table 1: Baseline demographics of participants enrolled in SYS6002-001 and the associated clinical characteristics of interest

Safety and Dose Modifications

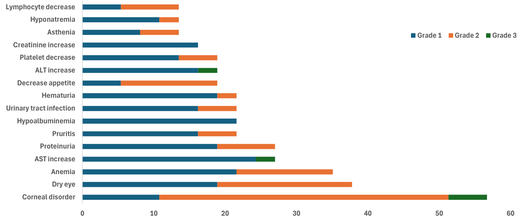


Figure 4: A summary of selected TEAEs either >20% or previously reported per CTCAEv5 criteria as of May 2024 cut off

- SYS6002 was generally well tolerated with mainly grade 1 or 2 AEs
- No DLTs or grade 4 or 5 AEs have been observed to date.
- Anemia and eye-related adverse events were the most common treatment emergent AEs (TEAEs)
- One patient had a grade 3 'rash' event which lasted for 8 days and did not result in a reduction or interruption in dose (2.7 mg/kg)
- Two grade related 3 SAEs (ILD and pulmonary infection) were reported in a single participant, and 1 grade 3 (ALT↑ with liver mets) in a separate participant
- To date 1 case of neuropathy was reported (numb hands) associated with grade 3 hypokalemia and it resolved after 10 days of therapy with both oral and parenteral K+ replacement therapy
- 2 grade 3 corneal disorders have been seen at 2.7mg/kg and 3.6mg/kg but not at the 4.5mg/kg dose where preventative eye measures were introduced

Dose modifications (N=37)	Value
Discontinuations	0
Reductions	0
Interruptions	1 (2.7%)

Table 2: A summary of the dose modifications observed in the SYS6002-001 trial

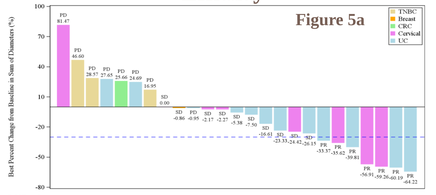
Clinical Pharmacology

- After single IV infusion of SYS6002, the exposure of TAb, ADC and MMAE generally increased in a dose proportional manner except MMAE at dose levels beyond 2.7 mg/kg
- Clearance and volume of distribution were similar across doses
- The half-lives of TAb, ADC and MMAE were 4-11 days, 4-9 days and 5-10 days, respectively
- No obvious or major accumulation was observed on C3D1
- Time to peak conc of MMAE was approx. 3-7 days
- When compared to EV exposures, SYS6002 (CRB-701) consistently demonstrates lower free MMAE exposure even after accounting for a lower DAR

Table 3: SYS6002 (CRB-701) exposure relative to EV at 1.25 mg/kg Q1W over 21-day dosing

21 Day PK	Comparison	Patients	%ADC		%Free MMAE	
		N	C_{max}	$AUC_{0\text{-}21d}$	C_{max}	$AUC_{0\text{-}21d}$
Enfortumab vedotin (EV) 1.25 mg/kg Q1Wx3	EV Benchark	--	100%	100%	100%	100%
SYS6002 (CRB-701) 1.2 mg/kg Q3W	Matched ADC dose	3	78%	103%	33%	29%
SYS6002 (CRB-701) 2.7 mg/kg Q3W	Matched MMAE dose	2-5	190%	217%	67%	72%
SYS6002 (CRB-701) 3.6 mg/kg Q3W	2.9-fold EV ADC dose	8-12	245%	324%	69%	79%
SYS6002 (CRB-701) 4.5 mg/kg Q3W	3.6-fold EV ADC dose	1	287%	428%	62%	64%

Efficacy



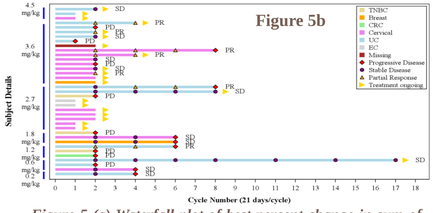


Figure 5 (a) Waterfall plot of best percent change in sum of diameters (%) and (b) Best Overall Response and a Swimmers plot of duration of therapy by dose level and subject as of May 2024

Discussion

- Participants spanned 5 tumor types and ranged from 35-76 years, with 70% being female
- A single UC patient at 3.6mg/kg was Nectin-4 negative
- SYS6002 (CRB-701) appears to be well tolerated
- Most AEs were grade 1 or 2 and reversible. Dose modifications were minimal, coinciding with a reduced role for skin rash and peripheral neuropathy
- Across the dose escalation SYS6002 (CRB-701) demonstrated approximately dose-proportional PK and minimal accumulation
- SYS-6002/CRB-701 exhibited a longer ADC half-life and a lower free-MMAE exposure relative to EV at comparable dose levels
- Anti tumor responses across multiple doses were observed, with the first confirmed stable disease at 0.6 mg/kg and the first confirmed partial response, at 1.2 mg/kg
- Responses available in mUC disease dosed ≥1.2mg/kg (n=9) suggest an emerging ORR of 44% and DCR of 78%
- Responses available in Cervical cancer patients dosed ≥1.2 mg/kg (n=7) suggest an emerging ORR of 43% and DCR of 86%
- Dose escalation is ongoing at 4.5 mg/kg Q3W
- Dose expansion is ongoing at both 2.7 & 3.6 mg/kg Q3W to further explore pharmacology and safety at these levels

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Abbreviations

TNBC (triple-negative breast cancer), CRC (colorectal cancer), DLT (dose limiting toxicity), SAE (serious adverse event), ILD (interstitial lung disease), AE (adverse event), TEAEs (treatment emergent adverse events), UC (urothelial cancer), Tab (total antibody), DCR (disease control rate), ORR (objective response rate)